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Is 1.25 mg Oral Fingolimod Effective In Reducing Relapses In Adults With Relapsing Multiple Sclerosis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2011

ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not is 1.25 mg oral fingolimod effective in reducing relapses in adults with relapsing multiple sclerosis.

STUDY DESIGN: Review of three English language primary studies published between 2006 and 2010.

DATA SOURCES: Randomized, double-blind, controlled clinical trials comparing daily 1.25 mg oral fingolimod to either identical placebo capsules or weekly intramuscular interferon beta-1a therapy were found using Pubmed and Cochrane Databases.

OUTCOMES MEASURED: Annualized relapse rate was assessed in all studies. Relapses were confirmed by neurologists and assessed using the Expanded Disability Status Scale (EDSS) to evaluate worsening symptoms. EDSS ranges from 0 (no disability) to 10 (death from multiple sclerosis). Adverse events were reported at every encounter between patients and treating physicians in Kappos et al. 2006. Independent data and safety monitoring boards were used to evaluate safety in Cohen et al. and Kappos et al. 2010, in these studies safety assessments were performed at set intervals throughout the studies.

RESULTS: Both Kappos et al. studies showed that 1.25 mg oral fingolimod was effective in reducing relapses in patients with relapsing multiple sclerosis compared to placebo. Cohen et al. demonstrated that 1.25 mg fingolimod was more effective in reducing relapses than the accepted therapy of interferon beta-1a injections. Adverse events were noted across all three studies. Patients in the 1.25 mg fingolimod groups were more likely to discontinue study due to serious adverse events compared to control groups. The most common serious adverse effects were bradycardia and atrioventricular block.

CONCLUSIONS: All studies showed that 1.25 mg oral fingolimod daily was effective in reducing relapses in patients with relapsing multiple sclerosis. Further studies are needed to assess the efficacy of fingolimod for other types of multiple sclerosis and to evaluate its effectiveness at various stages of disease progression. Adverse events have been associated with the use of fingolimod. Some of the noted effects are believed to be dose dependent.

KEY WORDS: Fingolimod, and Multiple Sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is a progressive neurological condition, characterized by demyelination of components of the central nervous system (CNS), including the brain, spinal cord, and optic nerves. Through this process, the nerves become damaged and scar tissue may form, contributing to patient disability. MS has a variety of presentations and severities depending on the specific nerve fibers and areas of the CNS that are affected. As a result, the exact symptoms and presentations associated with MS may be vague and differ among those affected with the disease.^{1,2}

There are four recognized courses of MS: relapsing-remitting, primary progressive, secondary progressive and progressive relapsing.^{1,2} Relapsing-remitting MS is the first course of 85% of those diagnosed with MS and consists of periods of declines in neurological function, called relapses, interspersed with remissions, or periods of symptom improvement without disease progression.² Primary progressive MS is a course defined by continuously declining neurological function from onset without evidence of remissions or exacerbations. Secondary progressive MS follows a previous diagnosis of relapsing-remitting MS and is characterized by more progressive and consistent worsening of symptoms that may or may not include periods of exacerbations, remissions, or stability. Progressive relapsing MS is a course of continuously worsening symptoms from onset with periods of exacerbations, without remissions.^{1,2}

It is estimated that multiple sclerosis affects about 2.5 million people globally and approximately 400,000 people in the United States.³ Although MS can present at any age, it is generally considered an adult-onset disease with the majority of patients diagnosed between ages 20-50.^{2,3} Although the number of healthcare visits made by patients with MS has not been officially recorded, patients with MS work with a collaboration of health professionals which can

include neurologists, nurses, physiatrists, physical therapists, occupational therapists, psychologists, speech language pathologists, social workers, and primary care practitioners.^{1, 2} “MS is estimated to cost the United States about \$28 billion annually in medical costs and lost productivity”.³

The exact cause of multiple sclerosis is still unknown; however it is believed that a combination of genetic, environmental and immunologic factors may be associated with the disease.^{1, 2} Although a specific genetic etiology has not been identified, there is evidence that individuals with first degrees relative with MS do have an increased risk of developing the disease compared to the general public.² Additionally, it has been noted that MS has a greater prevalence in regions of the world further from the equator, specifically past 40° latitude.^{1, 2} Recent research has also focused on a suspected autoimmune etiology, targeting lymphocytes as potential cells involved in the characteristic myelin damage associated with MS.^{4, 5, 6}

There is no cure for multiple sclerosis. Current management strategies include rehabilitation services to preserve and improve function, treatment of symptom exacerbations with high dose corticosteroids, and the use of disease modifying agents to reduce progression and exacerbations in patients with relapsing-remitting or secondary progressive disease.^{1, 2} Traditional disease modifying agents include glatiramer acetate, interferon beta-1a, interferon beta-1b, mitoxantrone, and natalizumab. These therapies are administered intravenously or through subcutaneous or intramuscular injections at intervals varying from daily to four times a year, depending on the agent.^{1, 7}

Fingolimod is the first oral disease modifying agent approved by the FDA for treatment of multiple sclerosis.¹ Fingolimod is a sphingosine-1-phosphate-receptor modulator that interferes with the release of lymphocytes from lymph nodes to prevent possible infiltration and

damage of the CNS by these cells.^{4,5,6} It has also been suggested that fingolimod may exhibit a neuroprotective or restorative role through its effect on the sphingosine-1-phosphate receptors of the affected neuronal cells.^{4,6}

OBJECTIVE

The objective of this systematic review is to determine whether or not “is 1.25 mg oral fingolimod effective in reducing relapses in adults with relapsing multiple sclerosis”?

METHODS

The criteria used for selection of studies included adult patients, 18 years or older, formally diagnosed with relapsing multiple sclerosis. Additional inclusion criteria varied slightly among the studies selected. Cohen et al. and Kappos et al. 2010 specified that patients meet the revised McDonald criteria, had a score of 0 to 5.5 on the Expanded Disability Status Scale (EDSS), and that patients either experienced at least one documented relapse during the previous year, or at least two documented relapses during the previous two years.^{4,6} Kappos et al. 2006 selected neurologically stable individuals with an EDSS score of 0 to 6, who either experienced two or more documented relapses within the past two years or had one documented relapse one year prior to enrollment and had one or more gadolinium-enhanced lesions on magnetic resonance imaging (MRI) at the time of screening.⁵

Each study excluded patients with documented relapse or corticosteroid treatment within 30 days.^{4,5,6} Cohen et al. and Kappos et al. 2010 also excluded those with active infection, macular edema, immunosuppression, or a clinically significant coexisting systemic disease.^{4,6} Kappos et al. 2010 additionally excluded those with diabetes mellitus and those who had used interferon-beta or glatiramer acetate therapy within three months.⁶ Kappos et al. 2006 also excluded individuals with immunomodulatory therapy within three months, white cell count of

less than $3500/\text{mm}^3$, lymphocyte count less than $800/\text{mm}^3$, or a history of cardiac conditions that might increase the risk of a decrease in heart rate.⁵ Kappos et al. 2006 specifically excluded patients with use of azathioprine or methotrexate within 6 months, cyclophosphamide within 12 months, or mitoxantrone or cladribine within 24 months.⁵

The intervention used in all studies was daily doses of 1.25 mg oral fingolimod. Results were compared to daily doses of an identical placebo capsule in Kappos et al. 2006 and 2010.^{5, 6} Cohen et al. compared results to weekly doses of 30 mcg intramuscular interferon beta-1a.⁴ The outcome measured in all three studies used was annual relapse rate, which was confirmed by neurologists using the EDSS.^{4, 5, 6} All three studies used in this review were double-blind randomized controlled trials with the intention to treat relapses in adult subjects previously diagnosed with relapsing multiple sclerosis.

Key words in the literature searches were fingolimod and multiple sclerosis. All articles were peer-reviewed from the New England Journal of Medicine and were published in English between 2006 and 2010. Literature searches were conducted using Pubmed and Cochrane databases. Articles were selected based on relevance and outcomes that mattered to patients (Patient Oriented Evidence that Matter, POEMs). Exclusion criteria included articles published prior to 1996 and participants under age 18. Included studies were randomized controlled trials with intention to treat, dated after 1996. Statistics used include *p* values, number needed to treat (NNT), number needed to harm (NNH), relative risk reduction (RRR), relative risk increase (RRI), absolute risk reduction (ARR), and absolute risk increase (ARI). Demographics of included studies are provided in Table 1.

Table 1: Table of demographics of included studies.

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Cohen 2010 ⁴	RCT	1292	18-55	Adults with relapsing-remitting MS, who met revised McDonald criteria, had an EDSS score of 0-5.5, and ≥ 1 relapse documented in previous year or ≥ 2 relapses documented in the previous 2 years	Documented relapse or corticosteroid treatment within 30 days, active infection, macular edema, clinically significant coexisting systemic disease, or immunosuppression	139	Daily doses of 0.5 mg, or 1.25 mg oral fingolimod VS. weekly doses of 30 mcg intra-muscular interferon beta-1a for 12months
Kappos 2006 ⁵	RCT	281	18-60	Adults with relapsing MS with and score of 0-6 on the EDSS, neurologically stable condition and ≥ 1 of the following: <ul style="list-style-type: none"> ≥ 2 documented relapses in the previous 2 years; or ≥ 1 documented relapses in the year before enrollment, and ≥ 1 gadolinium-enhanced lesions detected on MRI at screening 	Evidence of relapse within 30 days before or during screening or baseline phases, corticosteroid use within 30 days, immunomodulator therapy within 3 months, WBC count $< 3500/\text{mm}^3$, lymphocyte count $< 800/\text{mm}^3$, history of cardiac condition that may increase risk of reduced heart rate, or immune-suppressive therapy	26	Daily doses 1.25 mg or 5.0 mg fingolimod VS. daily doses of identical placebo capsule for 6 months
Kappos 2010 ⁶	RCT	1272	18-55	Adults with relapsing-remitting MS who met revised McDonald criteria, had an EDSS score of 0-5.5, and ≥ 1 relapse documented in the previous year or ≥ 2 relapses documented in the previous 2 years	Documented relapse or corticosteroid use within 30 days, active infection, macular edema, DM, clinically significant coexisting systemic, or immunosuppression	239	Daily doses of 0.5 mg, or 1.25 mg oral fingolimod VS. daily doses of identical placebo capsule for 24 months

OUTCOMES MEASURED

The outcome assessed in all three studies was the annual relapse rate, representing the number of confirmed relapses per year. Relapses were confirmed by neurologists and evaluated using the EDSS to assess worsening symptoms. In all studies, EDSS scores were monitored every 3 months. The EDSS is a widely used scale for assessing MS spanning from no disability (0) to death from MS (10). EDSS scores are based on neurological exam findings, functional system scores (FSS), observations, gait assessments and use of assistive devices.⁸ The FSS is an

additional rating scale, scoring from 0-6, that focuses on specific neurological systems including pyramidal, cerebellar, brainstem, sensory, visual, cerebral and bowel-bladder functions.⁸

There were slight differences in the definition of relapse among the selected studies.

Kappos et al. 2006 defined relapse as “the occurrence of new symptoms or worsening of previously stable or improving symptoms and signs not associated with fever, lasting more than 24 hours and accompanied by an increase of at least half a point in the EDSS score or 1 point for at least one of the functional systems, excluding the bowel- bladder and mental systems”.⁵ Cohen et al. defined relapse as “ new, worsening, or recurrent, neurological symptoms, that occurred at least 30 days after the onset of a preceding relapse, that lasted at least 24 hours without fever or infection, and accompanied by an increase of at least half a point on the EDSS or an increase of at least one point in two functional-systems scores or of at least two points in one functional-system score (excluding changes in bowel bladder function and cognition)”.⁴ Relapses in Kappos et al. 2010 needed to be associated with “an increase of at least half a point in the EDSS score, of 1 point in each of two EDSS functional system scores, or of 2 points in one EDSS functional-system score (excluding scores for the bowel-bladder or cerebral functional systems)”.⁶

In Kappos et al. 2006, adverse events were reported at all encounters between patients and treating physicians, including scheduled encounters at screening, baseline, days 1 and 7, and monthly for 6 months.⁵ Independent data and safety monitoring boards evaluated safety in Cohen et al. and Kappos et al. 2010. Safety assessments were performed at screening, baseline and months 1, 2, 3, 6, 9 and 12 in Cohen et al.⁴ Safety assessments occurred at screening, baseline, week 2, and months 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 in Kappos et al. 2010.⁶

RESULTS

In all studies, the results related to the efficacy of 1.25 mg fingolimod compared to the

respective controls were presented principally as dichotomous data and were further analyzed as dichotomous data. The data from each study were presented as an intention to treat analysis.

Both studies performed by Kappos et al. compared experimental groups using fingolimod therapy versus control groups taking identical placebo capsules. Kappos et al. 2006 reported the annualized relapse rate as 35% and 77% in the experimental and control groups, respectively ($p = 0.009$).⁵ The calculated RRR was -55%, and ARR was -42%. Based on the RRR and ARR the NNT for patients taking 1.25 mg fingolimod was estimated to be -3 (Table 2). The clinical relevance of this finding is that for approximately every 3 individuals using 1.25 mg fingolimod, there was one fewer incidence of relapse than in the control group.

Table 2. Efficacy of 1.25 mg Fingolimod for Reduction of Relapses in Multiple Sclerosis.

Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative Risk Reduction (RRR)	Absolute Risk Reduction (ARR)	Number Needed to Treat (NNT)	Statistical Significance
Kappos et al. 2006 ⁵	0.77	0.35	-0.55	-0.42	-2.4 (-3)*	P = 0.009
Kappos et al. 2010 ⁶	0.40	0.16	-0.60	-0.24	-4.2 (-5)*	P = <0.001 CI = 95%
Cohen et al. 2010 ⁴	0.33	0.20	-0.39	-0.13	-7.7 (-8)*	P = <0.001 CI = 95%

**Outcome measured was annual relapse; therefore, negative value for NNT signifies that for each number of participants taking 1.25 mg of fingolimod specified as NNT for each study there was one fewer incidence of relapse than in the control group.*

Kappos et al. 2010 reported the annualized relapse rate as 16% in the experimental group and 40% in the control group ($p = <0.001$; 95% CI).⁶ The calculated RRR was -60%, and ARR was -24%. Based on the RRR and ARR the NNT for patients taking 1.25 mg fingolimod was estimated to be -5, signifying that for about every 5 individuals using 1.25 mg fingolimod, there was one fewer incidence of relapse than in the control group (Table 2).

Cohen et al. compared groups taking fingolimod versus participants treated with beta-1a interferon used as a control. Cohen et al. reported the annualized relapse rate as 20% in the experimental group and 33% in the control group ($p = <0.001$; 95% CI).⁴ The calculated RRR was

-39%, and ARR was -13%. Based on the RRR and ARR the NNT for patients taking 1.25 mg fingolimod was estimated to be -8, signifying that for about every 8 individuals using 1.25 mg fingolimod, there was one fewer incidence of relapse than in the control group (Table 2).

Adverse events were noted across all three studies. Rates of any adverse event were similar between experimental 1.25 mg fingolimod compared to control groups in all studies. Kappos et al. 2006 reported occurrence of an adverse event in 84% of the experimental group and 82% of the control group.⁵ This difference is not statistically significant as no p-values were listed. The calculated RRI was 2%, and ARI was 2%. Based on the RRI and ARI the NNH for patients taking 1.25 mg fingolimod was 50 (Table 3). The clinical relevance of this finding is that for approximately every 50 individuals using 1.25 mg fingolimod, there is one additional occurrence of an adverse event compared to the control group.

Table 3. Occurrence of adverse events with use of 1.25 mg fingolimod.

Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative Risk Increase (RRI)	Absolute Risk Increase (ARI)	Number Needed to Harm (NNH)
Kappos et al. 2006 ⁵	0.82	0.84	0.02	0.02	50
Kappos et al. 2010 ⁶	0.93	0.94	0.01	0.01	100
Cohen et al. 2010 ⁴	0.92	0.91	-0.01	-0.01	-100*

**Negative value for NNH indicates that for every 100 patients in the control group, 1 additional patient will experience an adverse event compared to those receiving 1.25 mg fingolimod. P-values and 95% CI were not provided for this information.*

Kappos et al. 2010 reported adverse events in 94% of the 1.25 mg fingolimod group and 93% in the placebo group.⁶ This difference is not statistically significant as no p-values were listed. The calculated RRI and ARI was 1%. The calculated NNH for patients taking 1.25 mg fingolimod was 100; signifying that for about every 100 patients using 1.25 mg fingolimod, there is one additional occurrence of an adverse event compared to the control group (Table 3).

Cohen et al. reported occurrence of an adverse event in 90.5% of the group taking 1.25 mg fingolimod and 91.6% in the interferon beta-1a group.⁴ This difference is not statistically significant as no p-values were listed. The calculated RRI was -1.2%, and ARI was -1.1%. Based on the RRI and ARI the NNH for patients taking 1.25 mg fingolimod was -100 (Table 3). The clinical relevance of this finding is that for about every 100 individuals using the beta-1a interferon, there was one additional adverse event compared to those taking 1.25 mg fingolimod.

Patients in the 1.25 mg fingolimod groups were more likely to discontinue the studies due to serious adverse events compared to control groups.^{4,5,6} Kappos et al. 2006 had 5% of patients taking fingolimod 1.25 mg discontinue study due to adverse events compared with 4% taking placebo.⁵ Kappos et al. 2010 had 14% discontinue 1.25 mg fingolimod therapy due to adverse events compared to 7% of those taking placebo.⁶ Cohen et al. had 10% of patients taking fingolimod 1.25 mg discontinue study due to adverse events compared with 3.7% taking interferon beta-1a.⁴ P-values and 95% CI were not provided for this information.

Kappos et al. 2006 reported nasopharyngitis, dyspnea, headache, diarrhea and nausea as common occurring effects of fingolimod.⁵ Cohen et al. reported that the most common serious adverse events associated with 1.25 mg fingolimod therapy were bradycardia (2.4%) and atrioventricular (AV) block (1.2%).⁴ Decreased heart rate and first and second degree AV block were noted in all studies. Both occurred after initial fingolimod administration, were generally asymptomatic, and in most cases returned toward baseline with continued treatment.^{4,5,6}

The incidence of infection was similar between the experimental and control groups in Cohen et al. (51-53%) and Kappos et al. 2010 (69-72%).^{4,6} However, Cohen et al. did have 2 infection related fatalities in the 1.25 mg fingolimod group; one patient contracted disseminated primary varicella zoster, the other death resulted from herpes simplex encephalitis.⁴

Additionally, macular edema was also noted to occur in some patients taking 1.25 mg fingolimod in both Kappos et al. 2010 (2%), and Cohen et al. (1%).^{4, 6} Most of the cases were discovered within 4 months of therapy and resolved within 8 months of the discontinuation of therapy. No cases of macular edema were reported for any of the control groups.^{4, 6}

DISCUSSION

The current FDA approved dosage of fingolimod is 0.5 mg daily.⁹ This dose was also shown to be effective in reducing relapses and is suspected to have less adverse effects such as bradycardia and AV blocks, which are believed to be dose dependent effects on the sphingosine-1-phosphate receptors found in cardiac tissue.⁴ While the rate of infection was similar between experimental and control groups, there are warnings about possible immune suppression with the use of fingolimod.⁹ The articles used in this review did not examine the use of fingolimod for those younger than 18, nor is there any current dosing or recommendations for its use in this population. There are currently no listed contraindications to the use of fingolimod in the US.⁹

In 2008 the National Multiple Sclerosis Society noted that 43% of those with relapsing MS were not using disease modifying therapy, which could be detrimental as disease progression can still occur during remissions. Some suspected factors affecting patient access include the expense of therapies, lack of appropriate health coverage and restrictions by insurers including stipulations on which treatments are covered.⁷ However, the invasive nature of the current injectable treatments and their associated side effects should not be overlooked as a possible deterrent for proper adherence and access for some patients. Therefore, approval of oral therapy for relapsing MS may improve compliance and availability of treatment to some patients.⁴

A possible limitation to the assessments made in these studies involves the use of the EDSS. While the EDSS is a commonly used scale for MS clinical trials, it is based upon the

judgment of examiners which could provide for scoring variations among different evaluators.⁸

CONCLUSION

The studies reviewed support that 1.25 mg daily of oral fingolimod is effective for reducing relapses in relapsing MS. The two studies by Kappos et al. showed that fingolimod was effective compared to placebos. Cohen et al. demonstrated that daily oral fingolimod was more effective compared to the accepted intervention of weekly injections of interferon beta-1a. Further studies comparing the efficacy of fingolimod to other disease modifying agents could better support the use of fingolimod as a primary agent for relapsing MS.

The lengths of the studies differed ranging from 6 months to 2 years. Increasing the study lengths could provide more accurate information, as relapse frequency is unpredictable and long term effects may not be fully appreciated at the study lengths examined. While all patients evaluated had EDSS scores between 0-6, it was not noted how many patients from each EDSS level were in each study's experimental or control groups. Assessing smaller ranges of EDSS scores could more effectively demonstrate if fingolimod is more useful at reducing relapses at different stages of disease progression. These studies also only evaluated fingolimod for the treatment of relapsing MS. Presently, the INFORMS study is investigating the use of fingolimod for primary progressive MS; however there is need of more studies to examine the use of fingolimod for this and other forms of MS.¹⁰

The studies also demonstrated that there are potential adverse effects related to the use of fingolimod. However, the rate of adverse events was similar between control and experimental groups and some of the effects are suspected to be dose dependent. Further investigations may be required to evaluate the safety of fingolimod in specific populations or develop further advisories.

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